REMARKS

Claims 1-20 were pending in the subject application. By this Amendment, claims 1-12, 15, and 17-20 have been amended. Accordingly, upon entry of this Amendment, claims 1-20 will be pending.

Claims 1-12, 15, and 17-20 have been amended to correct a typographical error(s), to provide for more common claim language, and/or to more properly reflect the subject matter of the subject application.

Support for amended Claims 1 and 2 may be found in the specification at, inter alia, page 4, lines 27-34.

Support for amended Claims 12 and 20 may be found at, inter alia, original Claim 1.

Amended Claim 19 finds support at, inter alia, original Claim 11.

Amended Claims 3-11, 15 and 17-18 find support at, inter alia, each respective original claim.

Accordingly, no new matter has been added.

Claims 1 and 2 Are Definite

On page 2 of the Action, the Examiner rejected Claims 1 and 2 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. Specifically, the Examiner alleges that the phrase "an anion which does not interfere in an unfavorable way with the reaction" renders the scope of each claim unclear.

Without conceding the correctness of the Examiner's rejection, amended Claims 1 and 2 now recite in part:

> ...an anion that does not react as a nucleophile and does not compete with the indole for reaction with the 4-fluorophenylhalide, nor inactivates the copper catalyst.

Amended Claims 1 and 2 clearly define the present invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Claims 1-20 Are Not Obvious

On page 2 of the Action, the Examiner rejected Claims 1-20 under 35 U.S.C. §103(a), as being un-patentable over:

> Perregaard, et al. Journal of Medicinal Chemistry, 1992, 35:1092-1101 ("D1"); and
> Klapars, et al. Journal of the American Chemical Society, 2001, 123:7727-7729 ("D2"), or
> Kang, S.K., et al. Synlett, 2002, 3:427-430 ("D3"); in further view of
> Sarges, et al. Journal of Medicinal Chemistry, 1989, 32:437-444 ("D4").

The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of D2 or D3 with the teachings of D1 in further consideration of D4 to achieve the instant invention. The Examiner concludes that the experienced process chemist would be motivated to use this method because it is the preferred method, gives higher yields under

milder conditions, and leads to an important intermediate in the manufacture of a drug. See e.g., pages 4-6 of the Office Action.

Applicants respectfully disagree with the Examiner and maintain that any combination of D1 and D2, or D3, in further view of D4 does not render the present invention obvious to one skilled in the art.

For example, amended Claim 1 recites:

> A method for manufacture of sertindole comprising manufacturing 5-chloro-1-(4-fluorophenyl)-indole and converting it to sertindole, wherein the manufacturing ~~characterised in that the method for manufacture~~ of 5-chloro-1-(4-fluorophenyl)-indole comprises reacting 5-chloro-indole with a 4-fluorophenylhalide in the presence of a base, a chelating ligand and a catalytic ~~amounts~~ amount of a copper salt comprising copper(I) or copper(II), and an anion ~~which does not interfere in an unfavourable way with the reaction~~ that does not react as a nucleophile and does not compete with the indole for reaction with the 4-fluorophenylhalide, nor inactivates the copper catalyst.

The Examiner acknowledges that D1 prepared 5-chloro-1-(4-fluorophenyl)-indole (compound 10h of D1) by either Method C or D as per table II in D1, and not by Method A, which is the method of the present invention. See e.g., page 6 of the Office Action.

In fact, there is no motivation in D1 to use Method A for the production of the compound of the instant case, namely 5-chloro-1-(4-fluorophenyl)-indole. Even though D1 suggests that "[t]he Ullmann arylation procedure (method A, Scheme II) was preferred" (see page 1095, first paragraph), D1 teaches away from such Method A. For example, D1 provides:

Page 1095, third paragraph:

> Certain indoles (10) are **inaccessible** or at least **inconveniently** prepared by **methods A** or B in large-scale quantities...The 3-hydroxyindolines thus formed subsequently underwent acid-catalyzed water elimination **to the desired indoles** (10) **(method C**, Scheme II). The 5-CF3 (10f), 5-methylsulfonyl (10g) and **5-Chloro** (10h) **compounds were synthesized by method C** (table II).

Page 1095, fourth paragraph:

> Since indolin-3-ones were the key intermediates in **procedure C** we anticipated 3-acetoxyindoles 9 **to be more easily available precursors...**The resulting 3-hydroxyindolines eliminated water under the acidic conditions, as above, **to afford the desired indoles** (10) (Scheme II, **method D**). The **5-chloro (10h)**, 5-methoxy (10i), and 5-bromo (10j) **indoles were prepared accordingly** (Table II). **Method D appears to be the most versatile of the four methods in Scheme II.**

In other words, D1 teaches that 5-chloro-1-(4-fluorophenyl)-indole can be produced by Method C and D, both of which proceed in high yields (see e.g., the Experimental section of D1, pages 1099-1101). Method A, on the other hand, is not mentioned anywhere in D1 as being suitable for the production of 5-chloro-1-(4-fluorophenyl)-indole.

The authors of D1 are not just "skilled persons", but experts on the subject-matter of D1, and the teaching of these experts is clearly to choose either Method C or D for

producing 5-chloro-1-(4-fluorophenyl)-indole. Consequently, the skilled person searching for ways to produce 5-chloro-1-(4-fluorophenyl)-indole, **would not** have any reason to select Method A for producing 5-chloro-1-(4-fluorophenyl)-indole and thus, the instant invention.

Regarding D2, it fails to cure the deficiency of D1 with respect to making the instant invention obvious. For example, D2 discloses that the relatively electron-rich compounds 5-amino-, 5-methoxy- and 7-methyl-indole can be arylated with different aryl iodides, but D2 **fails to disclose or even discuss** the formation of the less electron-rich halogen-substituted arylation products, such as 5-chloro-1-(4-fluorophenyl)-indole of the instant invention.

However, D2 teaches that **aryl chlorides** may be used as arylation reagents (see D2 page 7728, right column, last paragraph), whereas D1 only teaches the **specific** use of the much **more reactive** aryl iodides (See e.g., page 1099, 3rd and 4th paragraphs of D1). Even though D2 teaches **aryl chlorides**, D2 does not teach nor suggest the use of indoles, much less 5-chloroindole as a starting reagent to produce 5-chloro-1-(4-fluorophenyl)-indole, the intermediate product of the present invention. Moreover, as both 5-chloroindole and the product 5-chloro-1-(4-fluorophenyl)-indole are themselves aryl chlorides, they are in principle capable of undergoing further reactions under the reaction conditions of D2.

If the skilled person (hereinafter referred as "he/him" for ease of reading) should be inclined somehow to combine the teachings of D1 and D2, he would receive no specific guidance as to using Method A for the production of 5-chloro-1-(4-fluorophenyl)-indole, but he would learn that aryl chlorides may act as arylation reagents under the reaction conditions found by the authors of D2. This new knowledge gained from D2 would likely cause him to speculate whether the proposed arylation reaction of 5-chloroindole would proceed selectively, or if side products could be formed to some extent as a result of further arylation reactions at the 5-

position of the indole nucleus. This speculation would probably cause him to return to D1 for a "safe solution" to the problem, and thus return him to the performed choice of the experts, Methods C and D.

For these reasons the skilled person would very likely favor Method C or D as a starting point for further development and scale-up work. Applicants respectfully note that the suggestion that a skilled person would choose Method A is a result of hindsight analysis. Applicants respectfully remind the Examiner that using hindsight in finding the instant invention obvious over prior art is impermissible. It is impermissible to use the Applicants' invention as a "road map" to piece together the teachings of the prior art in order to render the claimed invention obvious. See, e.g., MPEP §2142 (providing that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art"); see also, *KSR Int'l Co. v. Teleflex, Inc.*, at 22 (stating expressly that hindsight analysis of a patent challenged for obviousness is still to be avoided).

As previously presented, it is clear that D1 fails to provide any factual basis for teaching Method A as the means for producing 5-chloro-1-(4-fluorophenyl)-indole and fails to suggest an apparent reason to modify its teachings to achieve the present invention. And, the use of hindsight to find the present invention obvious over D1 with D2 is improper and is to be avoided.

Regarding D3, it also fails to cure the deficiency of D1 with respect to making the instant invention obvious. D3 teaches a copper-catalyzed reaction *N*-arylation of **aryl iodides** with benzamides or nitrogen heterocycles in the presence of a base, such as K_3PO_4 or Cs_2CO_3, and a ligand such as ethylenediame. See e.g., page 427 of D3.

However, D3 fails to teach the use of **aryl chlorides** as arylation reagents; rather D3 **only** teaches the use of the much more reactive **aryl iodides**. See title and Table 2. Although D3 teaches the treating 3,5-dimethyliodobenzene with indole, resulting in N-

aryl-substituted indole (see e.g., entry 5 of Table 2), D3 is silent on producing any other aryl-indoles, much less the 5-chloro-1-(4-fluorophenyl)-indole of the instant invention, which the Examiner acknowledges (see page 6, first paragraph of the Office Action).

Furthermore, there is no suggestion in D3, for one skilled in the art to use **aryl chlorides** as starting materials, much less 5-chloroindole, to arrive at the intermediate product 5-chloro-1-(4-fluorophenyl)-indole of the present invention. The motivation to modify prior art must arise from some teaching or suggestion in the art that provides the desirability to make such modification to arrive at a claimed invention. The mere fact that the prior art could be modified in such manner would not have made the modification obvious unless the prior art suggests the desirability of the modification, and D3 clearly **does not**. Thus, with the fact that D1 teaches away from Method A as previously discussed, the skilled person would not be motivated to combine the teachings of D1 and D3 to arrive at the instant invention. Rather, the skilled person would return to D1 to the performed choice of the experts, Methods C and D, and most probably select "the most versatile of the four methods", Method D.

Thus, one skilled in the art searching for a novel method for manufacturing 1-(4-fluorophenyl)-5-chloroindole would not have any reason to modify Method A taught in D1 in view of D3 to arrive at the method of the instant invention.

Regarding D4, it does not cure the deficiencies of D1 with D2 or D3 with respect to making the instant invention obvious. As noted by the Examiner, D4 teaches "a modified Ullmann reaction of **indole** with substituted **aryl iodides or bromides**." See e.g., page 6 of the Office Action and p. 438, paragraph 1 under "Chemistry").

However, D4 fails to teach the use of **aryl chlorides** as arylation reagents. D1 further fails to teach or suggest the reaction product, 1-(4-fluorophenyl)-5-chloro-

indole. See e.g., *id.* and Tables I-IV. Thus, without more, one the skilled person would not modify the teachings of D1 with those of D2 or D3 along with those of D4 o arrive to the method of the instant invention. Accordingly, the instant invention is not obvious in view of D1 and D2 or D3 in further view of D4.

In addition to the impermissible use of hindsight analysis previously noted, applicants also respectfully remind the Examiner that for the purpose of obviousness, it is impermissible to "pick and choose" from any reference only so much of it as to support a given position to the exclusion of other parts of the reference so as to limit the full appreciate of what the reference fairly suggests. See *In re Wesslau*, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965).

Furthermore, applicants respectfully acknowledge the Examiner's reminder that the skilled person is "one of ordinary creativity, not an automaton", that obviousness is not determined by a rigid formula and that common sense of the skilled person deems some inventions obvious. See page 8 of the Office Action (citing *Leapfrog v. Fisher-Price* and *KSR v. Teleflex* cases). However, applicants respectfully remind the Examiner that the Supreme Court in KSR v. Teleflex also reaffirmed the importance of avoiding mere conclusions as the only evidence to sustain a rejection under 35 U.S.C. § 103. *KSR International Co. v. Teleflex Inc.*, 550 U.S. __ (2007) ("rejections on obviousness grounds cannot be sustained on mere conclusory statements"). Thus, ordinary creativity and common sense of a skilled person should not be used as cover for mere conclusions and hindsight as basis for determining obviousness.

For the foregoing reasons, applicants respectfully request that the Examiner reconsider and withdraw the §103 rejection.

Applicants believe the subject application is in condition for allowance and earnestly solicit an early notice of same. If a telephone interview would be of assistance in

advancing prosecution of the above-identified application, applicants invite the Examiner to telephone the undersigned at the number provided below.

No additional fee, other than the fee for a three (3) months extension of time ($1,050.00), is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required or credit for overpayment due, authorization is hereby given to charge the respective amount to Deposit Account No. 503201.

Respectfully submitted,

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